Evaluation and Management of Alzheimer’s Dementia and related disorders: What is new in 2019?

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Objectives

To differentiate amongst the most common causes of dementia and understand diagnostic criteria and standard clinical evaluation.

To determine effective and safe treatments for the cognitive, functional and behavioral symptoms of dementia.

To appreciate current research approaches for disease modifying therapies to treat Alzheimer’s dementia.

2019 Alzheimer’s Disease Facts & Figures
The challenge began 100+ years ago

- November 1906: Dr. Alois Alzheimer presented first case in Germany
- 51-year-old Auguste D. had profound memory loss, confusion, language difficulty, unfounded suspicions about husband and hospital staff
- On autopsy: plaques and tangles, brain shrinkage, vascular changes
- Her young age made Alzheimer think Auguste had a rare disease associated with middle age

Pathology: Amyloid plaques

Pathology: Tau tangles

Image of neurofibrillary tangles (NFTs) from Wikipedia
Progression of Alzheimer’s Disease

Preclinical AD
- No clinical signs
- Unexplained pathology on CSF or PET
- May or may not progress to clinical AD

Prodromal AD
- Mild cognitive impairment (MCI)
- Minor changes in cognition, memory loss

Alzheimer’s Dementia
- Memory loss
- Cognitive impairment
- Behavioral changes
- Motor and speech dysfunction

Clinical Dementia
- Memory loss
- Cognitive impairment
- Behavioral changes
- Motor and speech dysfunction

Mild AD
Moderate AD
Severe AD

The Facts on Early Diagnosis and Disclosure

Only about 50% of people with Alzheimer’s are diagnosed.

Advantages of Early Diagnosis for Patient and Family
- Accept and cope with the diagnosis
- Learn to maximize capabilities
- Participate in care plans, advance directives
- Aid communication with family, physician
- Handle legal and financial arrangements
- Initiate prevention/treatment
- Adopt positive lifestyle changes
- Address safety concerns
- Participate in clinical trials
Risk Factors for Alzheimer’s Disease

- Age
- Genetics (APOE-4, Presenilin 1, 2 and APP)
- Down’s Syndrome
- Family History

Modifiable Risk Factors:
- Hypertension
- Diabetes
- Alcohol and Substance Abuse
- Depression
- Hyperlipidemia

Making the Diagnosis in the General Care Setting

Initial Assessment
- History from patient and family members/caregiver
- Relevant medical history; medication review
- Lab values: TSH, vitamins B12 and D, folate, CBC/Chem20

Screening for Memory Loss
- Cognitive screen
  - Tools available on the Alzheimer’s Pocketcard App
- Psychiatric screen

Referral to a Specialist
- Imaging to rule out other causes: CT, MRI
- Specialty referral: neurology, psychiatry, neuropsychology
- Specialized testing: FDG PET, Amyloid PET, CSF examination, APOE/genetic testing

Types of Dementia

- Vascular Dementia
- Dementia with Lewy Bodies
- Parkinson’s Disease
- Frontotemporal Dementia
- Huntington’s Disease
- Creutzfeldt-Jakob Disease
- Normal Pressure Hydrocephalus (NPH)
- Physical Injury to Brain
- Down Syndrome Dementia
- Korsakoff’s Syndrome
Treatable Causes of Cognitive Decline

- Vitamin B12, Vitamin D and folate deficiency
- Hypothyroidism
- Unstable medical problems: diabetes, heart failure
- Normal Pressure Hydrocephalus (NPH)
- Medication side effects: Tylenol PM (acetaminophen plus diphenhydramine)
- Excessive alcohol consumption

Montreal Cognitive Assessment (MoCA)

**Purpose**
- Used to detect mild cognitive impairment or early cognitive decline in about 15 minutes
- Not designed to indicate the severity of cognitive impairment

**Contents**
- Consists of a 30 point scale, a score of 26 or above is considered “normal”
- Assesses eight major cognitive domains:
  - Visuospatial/Executive
  - Naming
  - Memory
  - Attention
  - Language
  - Abstraction
  - Delayed Recall
  - Orientation

FDA Approved Therapies

**Cholinesterase Inhibitors:**
- Donepezil
- Rivastigmine
- Galantamine

**Glutamatergic agents:**
- Memantine
### Pharmacotherapy for AD

<table>
<thead>
<tr>
<th>Drug name (Brand name)</th>
<th>(stages)</th>
<th>FDA clearance date</th>
<th>Dosage</th>
<th>Adverse effects (&gt;10%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil (Aricept)</td>
<td>(all stages)</td>
<td>FDA Approval: 1996</td>
<td>5 mg PO in AM; may increase to 10 mg after 4-6 weeks</td>
<td>Nausea, diarrhea, insomnia, accident, infection</td>
</tr>
<tr>
<td>Rivastigmine (Exelon)</td>
<td>(all stages)</td>
<td>FDA Approval: 2000</td>
<td>Pill: Initial: 1.5 mg PO q12h Increase by 1.5 mg/dose q2 weeks Maintenance: 3.6 mg PO q12h Transdermal: Initial: 4.5 mg/24h (not therapeutic) Mild-moderate: 9.5-13.3 mg/24h Moderate-severe: 13.3 mg/24h</td>
<td>Nausea, vomiting, dizziness, diarrhea, headache, anorexia, abdominal pain</td>
</tr>
<tr>
<td>Galantamine (Razadyne)</td>
<td>(mild to moderate)</td>
<td>FDA Approval: 2001</td>
<td>Initial Conventional: 4 mg PO q12h ER: 8 mg PO qAM Maintenance (titrate at min 4 week intervals) Conventional: 8-12 mg PO q12h ER: 16-24 mg PO qAM</td>
<td>Nausea, diarrhea, vomiting</td>
</tr>
<tr>
<td>Memantine (Namenda)</td>
<td>(moderate to severe)</td>
<td>FDA Approval: 2003</td>
<td>Tablet: 5 mg PO once daily; increase by 5 mg/day each week to 20 mg/day PO qday ER: 7 mg PO qday; increase weekly to 28 mg PO</td>
<td>No AE over 10%. Dizziness (7%), confusion (6%), headache (6%)</td>
</tr>
<tr>
<td>Donepezil + Memantine (Namzaric)</td>
<td>(moderate to severe)</td>
<td>FDA Approval: 2014</td>
<td>memantine ER/donepezil: 28 mg/10 mg PO qday If stable on donepezil, titrate memantine by 7 mg increments</td>
<td>Nausea, diarrhea, insomnia, accident, infection</td>
</tr>
</tbody>
</table>

### Set Expectations

Some patients may experience clear benefit, all decline within 6-12 months

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![Graph showing ADAS-cog score improvement over months.](image-url)
Combination Therapy vs Monotherapy in AD dementia

2015 European Academy of Neurology Guidelines recommend combination of ChEI plus memantine rather than ChEI alone in patients with moderate to severe AD.1

Pooled data from 4 long-term trials (N=1549) demonstrated benefits of combination therapy vs monotherapy.2

Addition of memantine XR to stable dose of ChEI results in benefits in cognition and global function.3


Behavioral and Psychological Symptoms of Dementia (BPSD): Scope and Impact

- BPSD are common (90%+) and associated with caregiver burnout, long term care placement and elevated morbidity and mortality
- Changes in mood, perceptions, thought content or behavior in dementia are burdensome and costly to families and systems of care
- BPSD include: apathy, depression, agitation, sleep disturbance, irritability, anxiety, disinhibition, delusions (50%), hallucinations (25%)
- Half of patients with psychotic symptoms become aggressive toward others as a result of the symptoms
- BPSD may be due to dementia-related brain changes, co-morbid conditions (e.g. infection, pain, constipation) or may be responses to environmental conditions

Behavioral and Psychological Symptoms of Dementia (BPSD): Scope and Impact

- Practice guidelines recommend short-term use of antipsychotics first-line for agitation associated with psychotic features,1 yet side effects, including risk of stroke events and mortality impact treatment decisions
- Behavioral interventions widely accepted as first-line treatment, yet research is lagging behind and efficacy is modest for severe behavioral issues
- There are no FDA approved medications for the management of BPSD

Causes of Behavioral and Psychological Symptoms of Dementia

- **Environmental**
  - Caregiver interactions, time of day, change in routine, noise, cultural issues

- **Medical**
  - Pain, infection, constipation, electrolyte disturbance, unstable medical illness, poor sleep

- **Psychiatric**
  - Prior history of psychiatric illness (depression, anxiety disorder, bipolar disorder, Substance Use Disorder)

Medication therapy for BPSD

- No FDA approved therapies
- Antipsychotics (APs) modestly effective at reducing symptoms, but this comes at the price of side effects (sedation, orthostatic hypotension, ataxia, parkinson’s symptoms, Tardive Dyskinesia, metabolic syndrome, stroke risk and FDA warning for mortality)
- APA Consensus guidelines 2016 support short-term use of APs for severe agitation with psychosis not responding to behavioral interventions
- Other therapies include SSRIs (citalopram), mirtazapine and certain anticonvulsants but NOT benzodiazepines
- Experimental therapeutics for agitation
  - Dronabinol for AD with agitation (synthetic cannabinoid)
  - Electroconvulsive therapy (ECT) for severe agitation in AD

BPSD Management

- Non-pharmacologic strategies as first-line intervention:
  - Creating pleasurable or meaningful activities
  - Simplifying tasks
  - Enhancing communication
  - Very individualized

- Pharmacologic treatment of agitation and psychosis:
  - Citalopram 10-20 mg / Escitalopram 5-10 mg daily
  - Risperidone* 0.5-2 mg daily
  - Aripiprazole* 5-10 mg daily
  - Quetiapine* 25-200 mg daily
  - Olanzapine* 2.5-10 mg daily

* *Black box warning (increased mortality) and FDA warning (increased CVA risk) for all atypical antipsychotics
Early AD increases:
- Crash risk by as much as 7x
- Risk of becoming lost while driving
- Refer for road test:
  - MMSE < 24
  - MOCA < 18
- Affects attention span, visual-spatial ability, sequencing, cognitive mapping

Management Options:
- Counsel patient and care partner about risks
- Physician reporting voluntary in MA
- Advise patient to self-report serious impairment to RMV
- Consider legal advice and report to RMV Medical Affairs Branch
- Refer to AMA Ethical Opinion E-2.24
- Refer to certified driving evaluator to avoid patient conflict

Risk Management: Driving

Risk Management: Capacity/Decision Making
- Undue Influence / Elder Abuse
- Vulnerability to Coercion
- Finances
- Medication
- Decision Making
- Home Safety
  - Cooking
  - Firearms

Risk Management: Wandering
- Wandering and becoming lost is:
  - Common (60%)
  - Recurrent (75%)
  - Life threatening (40% mortality if not found)
  - Highly stressful for care partners
  - medicalert.org/safetreturn
Advanced Care Planning

- Living Will/Health Care Proxy
- Durable Power of Attorney
- Plan for changing care needs over course of disease
- Preferences for end-of-life care
  - Conversation Project Starter Kit for People with Dementia
- Care planning billable on CPT Code 99483
  - Billed in addition to extended E&M visit

Alzheimer’s Association

- Leading voluntary health organization in Alzheimer’s care, support, and research
- Mission
  - Eliminate Alzheimer’s disease through research
  - Provide and enhance care for all affected
  - Reduce risk of dementia through promotion of brain health
- 24/7 Helpline: 800-272-3900
- www.alz.org

Current Research

- Biomarkers
- Disease Modifying Therapeutics
- Lifestyle Modification
**Biomarkers: PET Imaging**

Positron Emission Tomography (PET)

- FDG measures brain activity; decreased with dementia
- Amyloid tracers detect amyloid without autopsy; increased in Alzheimer’s

**Biomarker Changes**

Adapted from Sperling et al, Alzheimer’s and Dementia, 2011.

All steps in β-amyloid production are potential targets

- Blocking the enzymes beta-secretase and gamma-secretase.
- Administering a “vaccine” to help the body clear beta-amyloid from the brain.
- Preventing beta-amyloid pieces from sticking together and forming plaques.

Aducanumab for MCI and Mild AD: Reduces amyloid plaque build-up in Brain


Two articles included: “In a business of highs and lows, biotech’s stock hits rock bottom” by Lary Edelman and “Caregivers’ hopes crushed as Biogen halts trials” by Felice J. Fryer and Jonathan Saltzman and Adam Feurstein
BAN2401

- Partnership between Eisai and Biogen
- Antibody targeting pre-plaque form of β-amyloid
- Phase 2b trial of 856 people
  - MCI due to AD
  - Mild AD
- Amyloid PET used to enroll and track results
- At highest dose tested:
  - 81% reverted from β-amyloid positive to negative
  - 30% reduction in rate of cognitive decline

Healthy Brain Aging:
Nutrition to Reduce Alzheimer’s Risks

- Eating foods typical of “Mediterranean Diet” Reduces Risk of AD by 40%
  (Columbia Univ, Scarmeas, Stern, Tang, Mayeux & Luchsinger 2006 & 2009)
- DASH Anti-Hypertensive Diet Lowers Risk of Dementia; Combination of Foods: Vegetables, Whole Grains, Nuts Legumes &, Low or No-fat Dairy (Wang et al. – 2009)
- Nutrients, in combination, lowering risk:
  - Nuts, fish, tomatoes, poultry, fruits, cruciferous & dark & leafy vegetables, salad dressing with oils, as well as, mono-, unsaturated fatty acids, omega 3’s, vitamin E, vitamin B12 & folate.
  - Low intakes of high-fat animal foods, i.e. dairy, red meat, organ meat and butter, and of saturated fats & Omega 6’s (Columbia Univ. 4 year study of 2,149 New Yorkers June 2010 Y. Gu, Scarmeas, et al. Arch of Neurol)

Healthy Brain Aging:
Exercise May Reduce ‘Senior Moments’

  - Moderate-intensity walking regimen or a stretching/toning program
  - Resistance training like weight lifting, aerobic training like walking, or balance and tone exercises, twice weekly for six months
- Increases brain cell growth in animals
- Increases brain blood flow in humans
Sleep and Alzheimer’s

- Sleep disordered breathing may speed up the progression of AD and Dementia
  - SDB has been found to be associated with higher levels of amyloid plaque and tau proteins in the brain
  - SDB may be a risk factor for AD
- SDB is treatable and early treatment could potentially delay the onset/progression of AD and All-cause Dementia
- Getting less than 7-8 hours of sleep a night has also been found to be associated with all-cause dementia
  - Getting the right amount of sleep may be a protective factor

The Lancet Commission 2017:
35% of all Dementia may be Preventable

- Early Life
  - Less Education
- Mid-Life
  - Hearing Loss
  - Hypertension
  - Obesity
- Late Life
  - Smoking
  - Social Isolation
  - Physical Inactivity
  - Diabetes
  - Late Life Depression

Research in Lifestyle Modification:
SPRINT MIND

- Hypertension
  - Sys BP >130 mmHg
- Additional CV risk factor
- Randomly assigned to
  - Standard: Systolic BP <140 mmHg
  - Intensive: Systolic BP <120 mmHg

<table>
<thead>
<tr>
<th></th>
<th>Intensive (n=4678)</th>
<th>Standard (n=4683)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) yrs, years</td>
<td>67.9 (0.4)</td>
<td>67.9 (0.5)</td>
</tr>
<tr>
<td>&gt;age 75%</td>
<td>28.2%</td>
<td>28.2%</td>
</tr>
<tr>
<td>Female</td>
<td>36.0%</td>
<td>35.2%</td>
</tr>
<tr>
<td>White</td>
<td>57.7%</td>
<td>57.7%</td>
</tr>
<tr>
<td>African-American</td>
<td>29.5%</td>
<td>30.4%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>10.3%</td>
<td>10.3%</td>
</tr>
<tr>
<td>Mean (SD) baseline BP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>139.1 (13.8)</td>
<td>139.7 (15.4)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>86.2 (11.9)</td>
<td>86.0 (12.8)</td>
</tr>
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</table>
Research in Lifestyle Modification: SPRINT MIND

Intensive treatment group:
- 19% reduction in MCI risk
- 15% reduction in combined risk of MCI and dementia
- Dramatic reduction in white matter lesions on MRI
- Immediate opportunity with life changing potential

Research in Lifestyle Modification

Two-year lifestyle intervention trial to support brain health and prevent cognitive decline in older individuals at increased risk for dementia

$20 million commitment from the Alzheimer’s Association

Reducing Risk for Cognitive Decline

- Physical activity
- Cardiovascular health
- Quit smoking
- Formal education
- Cognitive training
- Nutrition
- Social engagement
- Sleep
- Avoid brain injury
- Manage stress
Resources for Keeping up with Current Trials

- FDA.gov
- ClinicalTrials.gov
- alz.org/TrialMatch

Summary

- Early diagnosis of dementia is critical, more so with aging of the population and advent of disease modifying therapies
- Current treatments for dementia focus on cognitive, functional and behavioral symptoms
- Goal of treatment to stabilize symptoms, enhance quality of life and support caregiver all in an effort to enhance independence
- Prevention trials underway

Contact Information

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Opportunities to Participate in Clinical Research:
- Aniqa Rahman
  - arahman@mclean.harvard.edu
  - 617-855-2511

Memory Clinic referrals:
- Laurie Albanese
  - Albanel@partners.org
  - 617-855-3267

Other resources:
Alzheimer’s Association MA/NH:
- www.alz.org/manh/

Alzheimer’s Association TrialMatch
- www.alz.org